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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/989,730	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-138* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-138* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Status of Application, Amendments and/or Claims

The amendment filed 20 November 2001 has been entered in full. Claims 1-118 were cancelled. New claims 119-138 were added. Claims 119-138 are under examination.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 119-138 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

The instant claims are drawn to an isolated nucleic acid having various percent sequence identity to a nucleic acid sequence encoding the polypeptide shown in Figure 286 (SEQ ID NO:401), the nucleic acid sequence shown in Figure 285 (SEQ ID NO:400), the full length coding sequence of the cDNA deposited under ATCC accession number 203096, vector, and host cell.

The specification teaches that DNA62881-1515 sequence encodes a novel factor designated as PRO1185 (SEQ ID NO:401). The specification states that the cDNA clone (DNA62881-1515) that has been identified encodes a novel polypeptide having sequence identity to a glucose repression regulatory protein, tup1 (page 260, lines 17-21). The specification fails to disclose any information regarding ligands, functional characteristics/mechanisms of action of PRO1185. The specification only proposes a

sequence identity with the glucose repression regulatory protein, tup1. Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick *et al.* (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Karp (1998, Bioinformatics 14:753-754) states that functional annotations are propagated repeatedly from one sequence to the next with no record made of the source of a given annotation, leading to a potential transitive catastrophe of erroneous annotations. Incorrect functional predictions can result from a number of causes, including: divergence of function within homologous proteins, confusion or omission of functions across multimodular proteins or simply choosing the strongest homolog as the source of attributed function.

The specification asserts several utilities. The specification teaches that PRO1185 polypeptide encoding genes are amplified in the genome of certain human lung, colon and/or breast cancers and/or cell lines. The specification states that amplification is associated with overexpression of the gene product, indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers and diagnostic determination of the presence of those cancers (page 539, lines 20-25). The specification teaches experiments to determine whether the DNA encoding the PRO polypeptide is over-represented in any of the primary lung or colon cancers or cancer cell lines or breast cancer cell line that were screened. The starting material for the screen was genomic DNA isolated from a variety of cancers. As a negative control,

DNA was isolated from the cells of normal healthy individuals. The results of the TaqMan are reported in deltaCt units. One unit corresponds to 1 PCR cycle or approximately a 2 fold amplification relative to normal (page 539, lines 26-41). The specification states that the deltaCt values are used as quantitative measurement of the relative number of starting copies of a particular target sequence in a nucleic acid sample when comparing cancer DNA results to normal human DNA results (page 545, lines 6-9). The specification states that deltaCt values greater than or equal to 1.0 were reported (page 549, lines 3-5). The specification teaches that primary tumor (human lung tumor) LT3, LT26 and LT30 have deltaCt units of 1.01, 1.66 and 1.58 respectively for PRO1185 (page 552). The specification teaches that human colon cancer CT2 has a deltaCt unit of 1.73 for PRO1185 (page 552).

The instant specification does not provide a substantial utility *for nucleic acids encoding the polypeptide* because the increased copy number of DNA does not provide a readily apparent use for the polypeptide (there is no information regarding level of protein expression, activity or role in cancer). The protein is not specific to one tissue or type of tissue and is not associated with any disease or disorder. In addition, protein expression shows a poor correlation with mRNA expression. The Examiner has cited Haynes *et al.* to demonstrate this. Haynes *et al.* (Electrophoresis 19:1862-1871, 1998) studied 80 proteins relatively homogenous in half-life and expression level and found no strong correlation between protein and transcript levels; for some genes, equivalent mRNA levels translated into protein abundances which varied by more than 50-fold. Haynes concluded that the protein levels cannot be accurately predicted from the level

of the corresponding mRNA transcript (page 1863, 2nd paragraph, and Figure 1). Pennica *et al.* (Proc. Natl. Acad. Sci. 95:14717-1422, 1998) provides examples where copy number is amplified but the RNA expression is actually reduced. The relative gene copy number of WISP-2 is greatly amplified in human colon adenocarcinomas but the mRNA expression is significantly low (Figure 6 and Figure 7). Konopka *et al.* (abstract, Proc. Natl. Acad. Sci. 83:4049-52) states that protein expression of the abl polypeptide is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA.

The specification *also does not provide a substantial utility for isolated nucleic acids*. As was stated above, the specification discloses that the nucleic acid encoding PRO1185 had deltaCt values of at least 1.0 for a number of primary tumors. The specification explains how the deltaCt units correspond to amplification relative to normal tissue, but fails to disclose the significance of the deltaCt values. The specification teaches that PRO1185 is expressed in 3 out of 19 human lung tumor samples (LT3, LT26 and LT30) and 1 out of 17 human colon cancer samples (CT2). The deltaCt values for PRO1185 are less than 2 units. It is unclear to the Examiner if these results/values are considered significant, because the specification fails to teach or disclose art which teaches the guidelines for obtaining values of gene amplification in cancer cells. Most importantly, the Examiner is unable to find in the specification that the deltaCt data was corrected for aneuploidy. A slight amplification of a gene does not necessarily mean that the gene is overexpressed in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid, as amplification of proto-oncogenes

and aneuploidy is commonly observed in human tumors (Sen, Current Opinion in Oncology 12:82-88, 2000).

The assays recited in the specification are general utilities that would be applicable to the broad class of the invention. Processes to screen for receptor agonists and/or antagonists and making antibodies against polypeptides are not specific utilities. Agonist/antagonist assays are performed for any receptor-ligand pair when the physiological role of each is unknown. Antibodies can be made to any protein. The specification states that nucleotide sequences (or their complement) encoding PRO have various applications in the art including uses as hybridization probes, chromosome and gene mapping. These utilities are also general. A specific utility is a utility that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention.

The specification states that PRO polypeptides and antibodies to PRO polypeptides are useful as tools for screening compounds as drug candidates for diseases and nucleic acid encoding the PRO polypeptides may be used in gene therapy. The specification, however, fails to provide a correlation to the predisposition of a particular disease and the polypeptide and/or nucleic acid. For example is PRO1185 mutated, deleted or overexpressed in the disease? Using a protein, nucleic acid or an antibody to treat an unspecified disease or condition that has no particular correlation with a disease would not constitute a substantial utility. Further experimentation is required before this asserted utility is substantial.

The specification fails to disclose biological functions, physiological significance, or any specific and substantial utility of the claimed molecules. The instant application has failed to provide guidance as to how one of skill in the art could use the claimed invention in a way that constitutes a specific or substantial utility. Specific and substantial utilities amount to more than a starting point for further research and investigation. It does not require or constitute carrying out further research to identify or reasonably confirm what the practical use might ultimately be. The proposed uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the instant invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 119-138 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Furthermore, the instant claims are drawn to an isolated nucleic acid having at least 80% amino acid sequence identity to the a nucleic acid sequence encoding the polypeptide of SEQ ID NO:401, the nucleic acid sequence of SEQ ID NO:400 and the

full length coding sequence of the cDNA deposited under ATCC accession number 203096. There is no guidance in the specification or working examples showing what variant sequence is overexpressed in those specific tumors. If one skilled in the art were to make probes from the claimed variants, there is no guidance (or working examples) regarding what changes can be made without loss of probe specificity. In addition, the art fails to teach what variant sequences are amplified in various tumors.

Even if the PRO1185 polypeptide was shown to be correlated with a certain tumor, the instant claims would not be enabled because the specification fails to teach how to make variant nucleic acid sequences of SEQ ID NO:400 that would encode a polypeptide (SEQ ID NO:401), which could be used in cancer treatment (antagonist or agonist). As is well recognized in the art, any modification (even a "conservative" substitution) to a critical structural region of a protein is likely to significantly alter its functional properties. It is known for nucleic acids as well as proteins, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many cases (see Wells, 1990, Biochemistry 29:8509-8517). There is no guidance in the specification or working examples regarding what changes that can be made in the encoding sequence without loss of activity of the polypeptide.

The claims encompass an unreasonable number of inoperative nucleic acids, which the skilled artisan would not know how to use. The specification does not teach how to make any variant of the exemplified nucleic acid and provides no assay to evaluate the function. There are no working examples of nucleic acid sequences less than 100% identical to SEQ ID NO:400 or nucleic acid sequences less than 100%

identical to a nucleic acid sequence encoding polypeptides of SEQ ID NO:401, thus the skilled artisan would not know how to use non-identical nucleic acids on the basis of the teachings in the specification unless they possessed some sort of function, which the specification fails to teach.

For these reasons, which include the complexity and unpredictability of the nature of the invention and art in terms of the lack of knowledge about function of the encompassed nucleic acid sequence of SEQ ID NO:400 and nucleic acid sequence encoding the polypeptide of SEQ ID NO:401, the lack of working examples and the lack of direction or guidance for using non-identical nucleic acid sequence of SEQ ID NO:400 and nucleic acid sequences encoding polypeptides to SEQ ID NO:401, and the breadth of the claims which recite structure without function, it would require undue experimentation to the use the invention.

Claims 119-123, 130-138 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification provides adequate written description for SEQ ID NO:400 and SEQ ID NO:401, but not variants. The instant claims are drawn to nucleic acid having at least 80% to the nucleic acid sequence (SEQ ID NO:400), the nucleic acid sequence encoding the polypeptide (SEQ ID NO:401), and DNA hybridizing to the nucleic acid sequence (SEQ ID NO:400)

and the nucleic acid sequence encoding the polypeptide (SEQ ID NO:401) **with no stringency conditions**.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

With the exception of SEQ ID NO:400 and SEQ ID NO:401, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides and polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. In the absence of a recitation of clear hybridization conditions, the nucleic acid probe will hybridize with unrelated DNA sequences, corresponding sequences from other species, mutated sequences, allelic variants, splice variants and so forth. None of these sequences meet the written description provision of 35 USC 112, first paragraph.

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGF's were found to

be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated nucleic acids comprising the sequence set forth in SEQ ID NO:400 or isolated nucleic acids encoding the polypeptide sequence set forth in SEQ ID NO:401, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 119-125, 127, 128, 132-138 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 119-125, 127, 128, 132-138 are indefinite because they are drawn to an isolated nucleic acid sequence encoding various domains of the polypeptide disclosed in Figure 286 (SEQ ID NO:401). The specification states that the predicted polypeptide precursor is 198 amino acids long. The specification teaches that the signal peptide is about 1-21 of SEQ ID NO:401 (page 506, lines 1-6). The specification, however, fails to identify extracellular and/or transmembrane domains of the instant protein. Thus it is unclear how to discern a nucleic acid sequence encoding the extracellular domain or

the extracellular domain lacking its associated signal peptide. The metes and bounds of the instant claims cannot be determined.

Claims 132-134 are indefinite in its recitation of hybridization language without clear hybridization conditions. Stringency is relative, and the art does not recognize a single set of conditions as stringent. The specification also does not provide an unambiguous definition for the term. In the absence of a recitation of clear hybridization conditions (e.g., "hybridizes at wash conditions of A X SSC and B % SDS at CoC"), the claims fail to define the metes and bounds of the varying structures of polynucleotides recited in the claimed methods.

Priority

Priority of the instant application is denied because the priority does not meet the requirements of 35 USC 112, First Paragraph. Therefore, the effective filing date for the purposes of applying art is the same as the actual filing date.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical

Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 119-121 and 132-138 are rejected under 35 U.S.C. 102(e) as being anticipated by LeFleur *et al.*, US Patent No. 6,569,992. LeFleur *et al.* teach a nucleic acid sequence which is 90.4% identical to the instant nucleic acid sequence encoding the polypeptide (SEQ ID NO:401). Please see search query (Appendix A) and US Patent No. 6,569,992 (SEQ ID NO:16, columns 135-136). LeFleur *et al.* teach a nucleic acid that is 84.9% identical to the instant nucleic acid sequence (SEQ ID NO:400). Please see search query (Appendix B) and US Patent No. 6,569,992 (SEQ ID NO:16, columns 135-136). LeFleur *et al.* teach vectors, host cells and control sequences recognized by host cells (abstract; column 72, lines 16-67; column 73, lines 40-60). Because the instant claims lack hybridization conditions, the nucleic acid of LeFleur *et al.* would hybridize with the sequences of the instant invention (column 84, lines 15-25).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (571) 272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RMD
6/17/04

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